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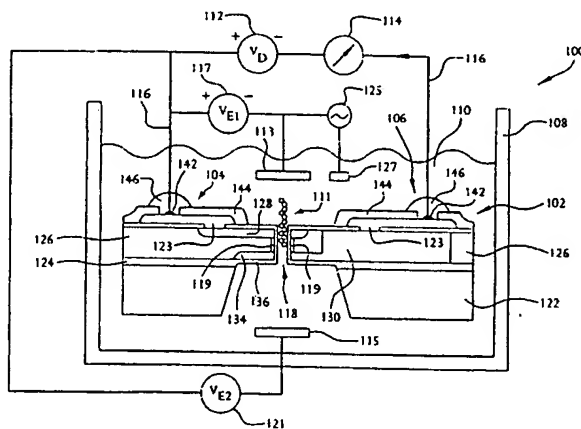
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(54) Title: FIELD EFFECT TRANSISTOR DEVICE FOR ULTRA-FAST NUCLEIC ACID SEQUENCING



(57) Abstract: A field effect transistor (FET), nucleic acid sequencing device (102) comprises source (106) and drain (104) regions, and gate oxide (136). The FET is formed from an SOI wafer comprising oxide layer (124) between silicon layers (122, 126). Potential is applied to the source and drain by voltage source (112) through leads (116) connected to the source/drain metal contacts (123, 142). The metal contacts are insulated from analyte solution in container (108) by insulating layers (144, 146). Additional electrodes (113, 115) powered by voltage sources (117, 121) and optional superimposed, high-frequency voltage source (125) or alternative acoustic wave generator (127) facilitate movement of nucleic acid strand (111) through opening (118). As nucleic acid strand (111) passes through opening (118) which serves as the gate electrode region, the charge representative of a nucleic acid base (adenine, thymine, guanine, or cytosine) modifies the current flowing between source (134) and drain (128) via channel (119) by modifying the electric field therebetween and is measured by ammeter (114). Device (102) may be used for sequencing other biological molecules.

FIELD EFFECT TRANSISTOR DEVICE FOR ULTRA-FAST NUCLEIC ACID SEQUENCING

The present application claims benefit under 35 U.S.C. § 119(e) of a provisional U.S. Patent Application of Jon R. Sauer et al. entitled "Ultra-Fast, Semiconductor-Based Gene Sequencing", Serial No. 60/199,130, filed April 24, 2000, and of a provisional U.S. Patent Application of Bart Van Zeghbroeck et al. entitled "Charge Sensing and Amplification Device for DNA Sequencing", Serial No. 60/217,681, filed July 12, 2000, and claims benefit under 35 U.S.C. § 120 of a non-provisional U.S. Patent Application of Jon R. Sauer et al. entitled "An Ultra-Fast Nucleic Acid Sequencing Device and a Method for Making and Using the Same", Serial No. 09/653,543, filed August 31, 2001, the entire contents of both of said provisional applications and said non-provisional application being incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to a system and method employing a semiconductor device having a detecting region for identifying the individual mers of long-chain polymers, such as carbohydrates and proteins, as well as individual bases of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and a method for making the semiconductor device. More particularly, the present invention relates to a system and method employing a semiconductor device, similar to a field-effect transistor device, capable of identifying the bases of a DNA/RNA strand to thus enable sequencing of the strand to be performed.

Description of the Related Art:

DNA consists of two very long, helical polynucleotide chains coiled around a common axis. The two strands of the double helix run in opposite directions. The two strands are held together by hydrogen bonds between pairs of bases, consisting of adenine (A), thymine (T), guanine (G), and cytosine (C). Adenine is always paired with thymine, and guanine is always paired with cytosine. Hence, one strand of a double helix is the complement of the other.

Genetic information is encoded in the precise sequence of bases along a DNA strand. In normal cells, genetic information is passed from DNA to RNA. Most RNA molecules are single stranded but many contain extensive double helical regions that arise from the folding of the chain into hairpin-like structures.

Mapping the DNA sequence is part of a new era of genetic-based medicine embodied by the Human Genome Project. Through the efforts of this project, one day doctors will be able to tailor treatment to individuals based upon their genetic composition, and possibly even correct genetic flaws before birth. However, to accomplish this task it will be necessary to sequence each individual's DNA. Although the human genome sequence variation is approximately 0.1%, this small variation is critical to understanding a person's predisposition to various ailments. In the near future, it is conceivable that medicine will be "DNA personalized", and a physician will order sequence information just as readily as a cholesterol test is ordered today. Thus, to allow such advances to be in used in everyday life, a faster and more economical method of DNA sequencing is needed.

One method of performing DNA sequencing is disclosed in U.S. Patent No. 5,653,939, the entire content of which is incorporated herein by reference. This method employs a monolithic array of test sites formed on a substrate, such as a semiconductor substrate. Each test site includes probes which are adapted to bond with a predetermined target molecular structure. The bonding of a molecular structure to the probe at a test site changes the electrical, mechanical and optical properties of the test site. Therefore, when a signal is applied to the test sites, the electrical, mechanical, or optical properties of each test site can be measured to determine which probes have bonded with their respective target molecular structure. However, this method is disadvantageous because the array of test sites is complicated to manufacture, and requires the use of multiple probes for detecting different types of target molecular structures.

Another method of sequencing is known as gel electrophoresis. In this technology, the DNA is stripped down to a single strand and exposed to a chemical that destroys one of the four nucleotides, for example A, thus producing a strand that has a random distribution of DNA fragments ending in A and labeled at the opposite end. The same procedure is repeated for the other three remaining bases. The DNA fragments are separated by gel electrophoresis according to length. The lengths show the distances from the labeled end to the known bases, and if there are no gaps in coverage, the original DNA strand fragment sequence is determined.

This method of DNA sequencing has many drawbacks associated with it. This technique only allows readings of approximately 500 bases, since a DNA strand containing more bases would "ball" up and not be able to be read properly. Also, as strand length increases, the resolution in the length determination decreases rapidly, which also limits analysis of strands to a length of 500 bases. In addition, gel electrophoresis is very slow and not a workable solution for the task of sequencing the genomes of complex organisms. Furthermore, the preparation before and analysis following electrophoresis is inherently expensive and time consuming. Therefore, a need exists for a faster, consistent and more economical means for DNA sequencing.

Another approach for sequencing DNA is described in U.S. Patent Nos. 5,795,782 and 6,015,714, the entire contents of which are incorporated herein by reference. In this technique, two pools of liquid are separated by a biological membrane with an alpha hemolysin pore. As the DNA traverses the membrane, an ionic current through the pore is blocked. Experiments have shown that the length of time during which the ionic current through the pore is blocked is proportional to the length of the DNA fragment. In addition, the amount of blockage and the velocity depend upon which bases are in the narrowest portion of the pore. Thus, there is the potential to determine the base sequence from these phenomena.

Among the problems with this technique are that individual nucleotides cannot, as yet, be distinguished. Also, the spatial orientation of the individual nucleotides is difficult to discern. Further, the electrodes measuring the charge flow are a considerable distance from the pore, which adversely affects the accuracy of the measurements. This is largely because of the inherent capacitance of the current-sensing electrodes and the large statistical variation in sensing the small amounts of current. Furthermore, the inherent shot noise and other noise

sources distort the signal, incurring additional error. Therefore, a need exists for a more sensitive detection system which discriminates among the bases as they pass through the sequencer.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a system and method for accurately and effectively identifying individual bases of DNA or RNA.

Another object of the present invention is to provide a system and method employing a semiconductor device for sequencing individual bases of DNA or RNA.

A further object of the present invention is to provide a method for manufacturing a semiconductor-based DNA or RNA sequencing device.

Another object of the present invention is to provide a system and method for accurately and effectively identifying the individual mers of long-chain polymers, such as carbohydrates or proteins, as well as measuring the lengths of the long-chain polymers.

Still another object of the present invention is to provide a system and method employing a semiconductor-based device having an opening therein, for accurately and effectively identifying bases of DNA or RNA by measuring charge at a location where the DNA or RNA molecules traverse the opening in the sequencer, to thus eliminate or at least minimize the effects of shot noise and other noise sources associated with the random movement of the DNA or RNA molecules through the opening.

These and other objects of the invention are substantially achieved by providing a system for detecting at least one polymer, comprising at least one semiconductor device having at least one detecting region which is adapted to detect a charge representative of a component of the polymer proximate to the detecting region. The component can include a base in a nucleic acid strand, so that the detecting region is adapted to detect the charge which is representative of the base in the nucleic acid strand. The detecting region is further adapted to generate a signal representative of the detected charge. Also, the detecting region can include a region of the semiconductor device defining a recess in the semiconductor device, or an opening in the semiconductor device having a cross-section sufficient to enable the polymer to enter the opening, so that the detecting region detects the charge of the component in the opening. Furthermore, the semiconductor device preferably further includes at least

two doped regions, and the detecting region can pass a current between the two doped regions in response to a presence of the component proximate to the detecting region.

The above and other objects of the invention are also substantially achieved by providing a method for detecting at least one polymer, comprising the steps of positioning a portion of the polymer proximate to a detecting region of at least one semiconductor device, and detecting at the detecting region a charge representative of a component of the polymer proximate to the detecting region. The component can include a base in a nucleic acid strand, so that the detecting step detects a charge representative of the base. The method further comprises the step of generating at the detecting region a signal representative of the detected charge. The detecting region can include a region of the semiconductor device defining a recess in the semiconductor device, or an opening in the semiconductor device having a cross-section sufficient to enable the polymer to enter the opening, so that the detecting step detects the charge of the component in the recess or opening. Furthermore, the semiconductor device can further include at least two doped regions, so that the method can further include the step of passing a current between the two doped regions in response to a presence of the component proximate to the detecting region.

The above and other objects of the invention are further substantially achieved by providing a method for manufacturing a device for detecting a polymer, comprising the steps of providing a semiconductor structure comprising at least one semiconductor layer, and creating a detecting region in the semiconductor structure, such that the detecting region is adapted to detect a charge representative of a component of the polymer proximate to the detecting region. The component can include a base in a nucleic acid strand, and the detecting region can be created to detect a charge representative of the base in the nucleic acid strand. The method can further include the step of creating a recess in the semiconductor structure, or creating an opening in the semiconductor structure having a cross-section sufficient to enable a portion of the polymer to pass therethrough, and being positioned in relation to the detecting region such that the detecting region is adapted to detect the charge representative of the component in the recess or opening. The method can further include the step of forming an insulating layer on a wall of the semiconductor layer having the opening to decrease the cross-section of the opening. Furthermore, the method can include the step of creating at least two doped regions in the semiconductor layer which are positioned with respect to the detecting region such that the detecting region is adapted to pass a current

between the doped regions in response to the component of the polymer proximate to the detecting region. The doped regions can be separated by a portion of the semiconductor layer having a different doping, and can be created as a stack of doped regions, each having a first doping and being separated by a layer having a second doping. The doped regions can include either a p-type or an n-type doping.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other objects, advantages and novel features of the invention will be more readily appreciated from the following detailed description when read in conjunction with the accompanying drawings, in which:

Figure 1 illustrates a system for performing DNA or RNA sequencing comprising a DNA or RNA sequencer constructed in accordance with an embodiment of the present invention;

Figure 2 illustrates a top view of the DNA or RNA sequencer shown in Figure 1;

Figure 3 is a graph showing an example of the waveform representing the current detected by a current detector in the system shown in Figure 1 as the adenine (A), thymine (T), guanine (G), and cytosine (C) bases of a DNA or RNA sequence pass through the DNA or RNA sequencer;

Figure 4 illustrates a cross-sectional view of a silicon-on-insulator (SOI) substrate from which a DNA or RNA sequencer as shown in Figure 1 is fabricated in accordance with an embodiment of the present invention;

Figure 5 illustrates a cross-sectional view of the SOI substrate shown in Figure 5 having shallow and deep n-type regions formed in the silicon layer, and a portion of the substrate etched away;

Figure 6 illustrates a cross-sectional view of the SOI substrate shown in Figure 5 in which a portion of the insulator has been etched away and another shallow n-type region has been formed in the silicon layer;

Figure 7 illustrates a cross-sectional view of the SOI substrate having an opening etched therethrough;

Figure 8 illustrates a top view of the SOI substrate as shown in Figure 7;

Figure 9 illustrates a cross-sectional view of the SOI substrate shown in Figure 7 having an oxidation layer formed on the silicon layer and on the walls forming the opening therein;

Figure 10 illustrates a top view of the SOI substrate as shown in Figure 9;

Figure 11 illustrates a detailed cross-sectional view of the SOI substrate shown in Figure 7 having an oxidation layer formed on the silicon layer and on the walls forming the opening therein;

Figure 12 illustrates a top view of the SOI substrate shown in Figure 11;

Figure 13 illustrates a detailed cross-sectional view of an exemplary configuration of the opening in SOI substrate shown in Figure 7;

Figure 14 illustrates a top view of the opening shown in Figure 13;

Figure 15 illustrates a cross-sectional view of the SOI substrate as shown in Figure 9 having holes etched in the oxidation layer and metal contacts formed over the holes to contact the shallow and deep n-type regions, respectively;

Figure 16 illustrates a cross-sectional view of the DNA or RNA sequencer shown in Figure 1 having been fabricated in accordance with the manufacturing steps shown in Figures 4-15;

Figure 17 illustrates a top view of a DNA or RNA sequencer having multiple detectors formed by multiple n-type regions according to another embodiment of the present invention;

Figure 18 illustrates a cross-sectional view of a DNA or RNA sequencer according to another embodiment of the present invention;

Figure 19 illustrates a cross-sectional view of a DNA or RNA sequencer according to a further embodiment of the present invention;

Figure 20 illustrates a cross-sectional view of a DNA or RNA sequencer according to a further embodiment of the present invention; and

Figure 21 illustrates a top view of the DNA or RNA sequencer shown in Figure 20.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figures 1 and 2 illustrate a system 100 for detecting the presence of a polymer, such as DNA or RNA, a protein or carbohydrate, or a long chain polymer such as petroleum, and, more preferably, for identifying the individual mers of the polymer or long chain polymer, as well as the length of the polymer or long chain polymer. The system 100 is preferably adaptable for performing sequencing of nucleic acids, such as DNA or RNA sequencing, according to an embodiment of the present invention. Accordingly, for purposes of this description, the system 100 will be discussed in relation to nucleic acid sequencing.

The system 100 includes a nucleic acid sequencing device 102 which, as described in more detail below, is a semiconductor device. Specifically, the nucleic acid sequencing device 102 resembles a field-effect transistor, such as a MOSFET, in that it includes two doped regions; a drain region 104 and a source region 106. However, unlike a MOSFET, the nucleic acid sequencing device does not include a gate region for reasons discussed below.

The nucleic acid sequencing device 102 is disposed in a container 108 that includes a liquid 110 such as water, gel, a buffer solution such as KCL, or any other suitable solution. It is important to note that the solution 110 can be an insulating medium, such as oil, or any other suitable insulating medium. In addition, the container 108 does not need to include a medium such as a liquid. Rather, the container 108 can be sealed and evacuated to create a vacuum in which nucleic acid sequencing device 102 is disposed. Also, although Figure 1 shows only a single nucleic acid sequencing device 102 in the container 108 for exemplary purposes, the container can include multiple nucleic acid sequencing devices 102 for performing multiple DNA sequencing measurements in parallel.

The liquid 110 or other medium or vacuum in container 108 includes the nucleic acid strands or portions of nucleic acid strands 111 to be sequenced by nucleic acid sequencing device 102. As further shown, voltage source 112, such as a direct current voltage source, is coupled in series with a current meter 114 by leads 116 across drain and source regions 104 and 106, respectively. In this example, the positive lead of voltage source 112 is coupled to the drain region 104 while the negative lead of voltage source 112 is coupled via the current meter 114 to source region 106.

The voltage potential applied across drain and source regions 104 and 106 of nucleic acid sequencing device 102 can be small, for example, about 100 mV, which is sufficient to create a gradient across drain and source regions 104 and 106, to draw the nucleic acid

strands into opening 118 of the nucleic acid sequencing device 102. That is, the nucleic acid strands 111 move through the opening 118 because of the local gradient. Alternatively or in addition, the liquid can include an ionic solution. In this event, the local gradient causes the ions in the solution to flow through the opening 118, which assists the nucleic acid strands 111, such as DNA or RNA, to move through the opening 118 as well.

Additional electrodes 113 and 115 positioned in the medium 110 and connected to additional voltage sources 117 and 121 would further facilitate the movement of the nucleic acid strands towards the opening 118. In other words, the external electrodes 113 and 115 are used to apply an electric field within the medium 110. This field causes all of the charged particles, including the nucleic acid strand 111, to flow either toward the opening 118 or away from the opening 118. Thus electrodes 113 and 115 are used as a means to steer the nucleic acid strands 111 into or out of the opening 118. In order to connect voltage sources 112 and 117 to the nucleic acid sequencer 102, metal contacts 123 are coupled to the n-type doped region 128 and 130, described in more detail below. The electrodes 113 and 115 could also provide a high frequency voltage which is superimposed on the DC voltage by an alternating voltage source 125. This high frequency voltage, which can have a frequency in the radio frequency range, such as the megahertz range (e.g., 10 MHz), causes the nucleic acid strand 111 and ions to oscillate. This oscillation makes passage of the nucleic acid strand 111 through the opening 118 smoother, in a manner similar to shaking a salt shaker to enable the salt grains to pass through the openings in the shaker. Alternatively, a device 127, such as an acoustic wave generator, can be disposed in the liquid 110 or at any other suitable location, and is controlled to send sonic vibrations through the device 102 to provide a similar mechanical shaking function.

As can be appreciated by one skilled in the art, the nucleic acid strands each include different combinations of bases A, C, G and T, which each contain a particular magnitude and polarity of ionic charge. The charge gradient between drain and source regions 104 and 106, or otherwise across the opening 118, will thus cause the charged nucleic acid strands to traverse the opening 118. Alternatively, another voltage source (not shown) can be used to create a difference in voltage potential between the opening 118 and the liquid. Also, a pressure differential can be applied across the opening 118 to control the flow of the DNA independent from the voltage applied between the source and drain 104 and 106.

In addition, the Sequencing device 102 can attract the nucleic acid strands to the opening 118 by applying a positive voltage to the medium 110 relative to the voltage source 112. Furthermore, the nucleic acid strands in the medium 110 can be pushed in and out of the opening 118 and be analyzed multiple times by reversing the polarity across drain and source regions 104 and 106, respectively.

As described in more detail below, the opening 118 is configured to have a diameter within the nanometer range, for example, within the range of about 1 nm to about 10 nm. Therefore, only one DNA strand can pass through opening 118 at any given time. As a DNA strand passes through opening 118, the sequence of bases induce image charges which form a channel 119 between the drain and source regions 104 and 106 that extends vertically along the walls of the device defining opening 118. As a voltage is applied between the source 136 and drain 128 by means of the voltage source 112, these image charges in the channel flow from source to drain, resulting in a current flow which can be detected by the current meter 114. The current exists in the channel as long as the charge is present in the opening 118, and thus the device current detected by the current meter 114 is much larger than the current associated with the moving charge. For example, a singly charged ion passing through the opening 118 accounts for an ion current of 0.16 pA and a device current of 160 nA.

Alternatively, the bases induce a charge variation in channel 119, leading to a current +variation as detected by current meter 114. Any variation of the ion flow through the opening due to the presence of the DNA strand would also cause a variation to the image charge in the channel 119 and results in a current variation as detected by current meter 114. That is, the device current measured by current meter 114 will diminish from, for example, 80 μ A to 4 μ A, as the DNA strand 111 passes through opening 118.

Each different type of bases A, C, G, and T induces a current having a particular magnitude and waveform representative of the particular charge associated with its respective type of bases. In other words, an A type base will induce a current in a channel between the drain and source regions of the nucleic acid sequencing device 102 having a magnitude and waveform indicative of the A type base. Similarly, the C, T and G bases will each induce a current having a particular magnitude and waveform.

An example of a waveform of the detected current is shown in Figure 3, which symbolically illustrates the shape, magnitude, and time resolution of the expected signals generated by the presence of the A, C, G and T bases. The magnitude of current is typically

in the microampere (μA) range, which is a multiplication factor of 10^6 greater than the ion current flowing through the opening 118, which is in the picoampere range. A calculation of the electrostatic potential of the individual bases shows the complementary distribution of charges that lead to the hydrogen bonding. For example, the T-A and C-G pairs have similar distributions when paired viewed from the outside, but, when unpaired, as would be the case when analyzing single-stranded DNA, the surfaces where the hydrogen bonding occurs are distinctive. The larger A and G bases are roughly complementary (positive and negative reversed) on the hydrogen bonding surface with similar behavior for the smaller T and C bases.

Accordingly, as the DNA strand passes through opening 118, the sequence of bases in the strand can be detected and thus ascertained by interpreting the waveform and magnitude of the induced current detected by current meter 114. The system 100 therefore enables DNA sequencing to be performed in a very accurate and efficient manner.

Since the velocity of the electrons in the channel 119 is much larger than the velocity of the ions passing through the opening, the drain current is also much larger than the ion current through the opening 118. For an ion velocity of 1 cm/s and an electron velocity of 10^6 cm/s, an amplification of 1 million can be obtained.

Also, the presence of a DNA molecule can be detected by monitoring the current I_p through the opening 118. That is, the current I_p through the opening reduces from 80 pA to 4 pA when a DNA molecule passes through the opening. This corresponds to 25 electronic charges per microsecond as the molecule passes through the opening.

Measurement of the device current rather than the current through the opening has the following advantages. The device current is much larger and therefore easier to measure. The larger current allows an accurate measurement over a short time interval, thereby measuring the charge associated with a single DNA base located between the two n-type regions. In comparison, the measurement of the current through the opening has a limited bandwidth, limited by the shot-noise associated with the random movement of charge through the opening 118. For example, measuring a 1 pA current with a bandwidth of 10 MHz yields a noise current of 1.8 pA. Also, the device current can be measured even if the liquids on both sides of the opening 118 are not electrically isolated. That is, as discussed above, the Sequencing device 102 is immersed in a single container of liquid. Multiple sequencers 102 can thus be immersed in a single container of liquid, to enable multiple current measurements

to be performed in parallel. Furthermore, the nanometer-sized opening 118 can be replaced by any other structure or method which brings the DNA molecule in close proximity to the two n-type regions, as discussed in more detail below.

The preferred method of fabricating a nucleic acid sequencing device 102 will now be described with reference to Figures 4-16. As shown in Figure 4, the fabrication process begins with a wafer 120, such as a silicon-on-insulator (SOI) substrate comprising a silicon substrate 122, a silicon dioxide (SiO_2) layer 124, and a thin layer of p-type silicon 126. In this example, the silicon substrate 122 has a thickness within the range of about 300 μm to about 600 μm , the silicon dioxide layer 124 has a thickness within the range of about 200 to 6400 nm, and the p-type silicon layer 126 has a thickness of about 1 μm or less (e.g., within a range of about 100 nm to about 1000 nm).

As shown in Figure 5, a doped n-type region 128 is created in the p-type silicon layer 126 by ion implantation, and annealing or diffusion of an n-type dopant, such as arsenic, phosphorous or the like. As illustrated, the n-type region 128 is a shallow region which does not pass entirely through p-type silicon 126. A deep n-type region 130 is also created in the p-type silicon 126 as illustrated in Figure 5. The deep n-type region 130 passes all the way through the p-type silicon 126 to silicon dioxide 124 and is created by known methods, such as diffusion, or ion implantation and annealing of an n-type material which can be identical or similar to the n-type material used to create n-type region 128. As further illustrated in Figure 5, the silicon substrate 122 is etched along its (111) plane by known etching methods, such as etching in potassium hydroxide (KOH) or the like. The back of the substrate 112 can also be etched with a teflon jig. As illustrated, the etching process etches away a central portion of silicon substrate 122 down to the silicon dioxide 124 to create an opening 132 in the silicon substrate 122.

As shown in Figure 6, the portion of the silicon dioxide 124 exposed in opening 132 is etched away by conventional etching methods, such as etching in hydrofluoric acid, reactive etching or the like. Another shallow n-type region 124 is created in the area of the p-type silicon 126 exposed at opening 132 by known methods, such implantation or diffusion of an n-type material identical or similar to those used to create n-type regions 128 and 130.

Opening 118 (see Figures 1 and 2) is then formed through the n-type region 128, p-type silicon 126 and bottom n-type region 134 as shown, for example, in Figures 7 and 8 by reactive ion etching (RIE) using Freon 14 (CF_4), optical lithography, electron-beam

lithography or any other fine-line lithography, which results in an opening having a diameter of about 10 nm. As shown in Figure 9, the diameter of the opening can be further decreased by oxidizing the silicon, thus forming a silicon dioxide layer 136 over the p-type silicon layer 126 and the walls forming opening 118. This oxidation can be formed by thermal oxidation of the silicon in an oxygen atmosphere at 1000°C, for example. As shown in detail in Figs. 11 and 12, the resulting oxide has a volume larger than the silicon consumed during the oxidation process, which further narrows the diameter of opening 118. It is desirable if the diameter of opening 118 can be as small as 1 nm.

Although for illustration purposes Figs. 1, 2 and 3-9 show opening 118 as being a cylindrically-shaped opening, it is preferable for opening 118 to have a funnel shape as shown, for example, in Figs. 13 and 14. This funnel-shaped opening 118 is created by performing V-groove etching of the (100) p-type silicon layer 126 using potassium hydroxide (KOH), which results in V-shaped grooves formed along the (111) planes 138 of the p-type silicon 126. The V-shaped or funnel-shaped opening, as shown explicitly in Figure 14, facilitates movement of a DNA strand through opening 118, and minimizes the possibility that the DNA strand will become balled up upon itself and thus have difficulty passing through opening 118. Oxidation and V-groove etching can be combined to yield even smaller openings. Additionally, anodic oxidation can be used instead of thermal oxidation, as described above. Anodic oxidation has the additional advantage of allowing for monitoring of the opening size during oxidation so that the process can be stopped when the optimum opening size is achieved.

Specifically, the opening 118 should be small enough to allow only one molecule of the DNA strand 111 to pass through at one time. Electron-Beam lithography can yield an opening 118 as small as 10 nm, but even smaller openings are needed. Oxidation of the silicon and V-groove etching as described above can be used to further reduce the opening to the desired size of 1-2 nm. Oxidation of silicon is known to yield silicon dioxide with a volume which is about twice that of the silicon consumed during the oxidation. Oxidation of a small opening 118 will result in a gradually reduced opening size, thereby providing the desired opening size. V-groove etching of (100) oriented silicon using KOH results in V-grooves formed by (111) planes. KOH etching through a square SiO₂ or Si₃N₄ mask results in a funnel shaped opening with a square cross-section. Etching through the thin silicon layer results in an opening 118 on the other side, which is considerable smaller in size.

Oxidation and V-groove etching can also be combined to yield even smaller openings 118. Anodic oxidation can be used instead of thermal oxidation, which has the additional advantage of enabling the size of the opening 118 to be monitored during the oxidation and the oxidation can be stopped when the appropriate size of the opening 118 is obtained.

Turning now to Figure 15, holes 140 are etched into the silicon dioxide 136 to expose n-type region 128 and n-type region 130. Metal contacts 142 are then deposited onto silicon dioxide layer 136 and into holes 140 to contact the respective n-type regions 128 and 130. An insulator 144 is then deposited over metal contacts 142 as shown in Figure 16, thus resulting in device 102 as shown in Figure 1.

As further shown in Figure 1, a portion of insulator 144 can be removed so that leads 116 can be connected to the n-type regions 128 and 130, which thus form the drain regions 104 and source 106, respectively. An additional insulator 146 is deposited over insulator 144 to seal the openings through which leads 116 extend to contact n-type regions 128 and 130. The completed device 102 can then be operated to perform the DNA sequencing as discussed above.

To identify the bases of the DNA molecule, it is desirable to measure a single electronic charge. If the sequencing device 102 is made to have a length and width of 0.1 by 0.1 μm , and the thickness of the silicon dioxide layer is 0.1 μm along the walls of the opening 118, a capacitance of 0.35 fF, a voltage variation of 0.45 mV, a device transconductance of 1 mS and a current variation of 0.5 nA are realized. Accordingly, a sequencing device 102 having these dimensions and characteristics can be used to detect a single electronic charge. The sequencing device 102 can further be reduced in size to obtain a sufficient special resolution to distinguish between different nucleotides.

Additional embodiments of the device 102 can also be fabricated. For example, Figure 17 illustrates a top view of a nucleic acid sequencing device according to another embodiment of the present invention. In this embodiment, the steps described above with regard to Figs. 3 through 16 are performed to form the n-type regions which ultimately form the drain and source regions. However, in this embodiment, the n-type region 128 shown, for example, in Figure 5, is formed as four separate n-type regions, 150 in a p-type silicon layer similar to p-type silicon layer 126 described above. A silicon dioxide layer 152 covers the p-type silicon layer into which n-type regions 150 have been created. Holes 156 are etched into silicon dioxide layer 152 so that metal contacts 158 that are deposited on silicon dioxide layer

152 can contact n-type regions 150. By detecting current flowing between the four drain regions formed by n-type regions 150 and the source region (not shown), the spatial orientation of the bases on the DNA strand passing through opening 152 can be detected.

Figure 18 is a cross section of a nucleic acid sequencing device 160 according to another embodiment of the present invention. Similar to nucleic acid sequencing device 102, 160 includes a silicon substrate 162, a silicon dioxide layer 164, an n-type region 166 implanted in p-type silicon 168, and a second n-type region 170 implanted in p-type silicon 168. Nucleic acid sequencing device 160 further has an opening 172 passing therethrough. The opening can be cylindrical, or can be a V-shaped or funnel-shaped opening as described above. A silicon dioxide layer 174 covers p-type silicon layer 168, n-type region 170 and n-type region 166 as shown, and decreases the diameter of opening 172 in the manner described above. An opening is etched into silicon dioxide layer 174 to allow a lead 176 to be attached to n-type region 170. Another lead 176 is also attached to an exposed portion of n-type region 166, so that a voltage source 178 can apply a potential across the drain region 180 formed by n-type region 170 and source region 182 formed n-type region 166. The nucleic acid sequencing device 160 can thus be used to detect the bases of a DNA strand 182 in a manner described above.

Figure 19 illustrates a DNA sequencing system 186 according to another embodiment of the present invention. System 186 includes a multi-layer nucleic acid sequencing device 188 which, in this example, comprises three MOSFET-type devices stacked on top of each other. That is, device 188 includes a silicon substrate 190 similar to silicon substrate 122 described above. A silicon dioxide layer 192 is present on silicon substrate 190. The device 188 further includes an n-type doped silicon region 194, a p-type silicon dioxide region 196, an n-type doped silicon region 198, a p-type silicon dioxide region 200, an n-type doped region silicon region 202, a p-type silicon dioxide region 204 and an n-type doped silicon region 206. Regions 194 through 206 are stacked on top of each other as shown explicitly in Figure 19. However, as can be appreciated by one skilled in the art, the polarity of the layers can be reversed for this embodiment, and for any of the other embodiments discussed herein. That is, the device 188 can comprise a p-type doped silicon region 194, an n-type silicon dioxide region 196, a p-type doped silicon region 198, and so on.

Additionally, a thin silicon dioxide layer 208 is formed over the layers as illustrated, and is also formed on the walls forming opening 210 to decrease the diameter of opening 210

in a manner described above with regard to opening 118. Also, opening 210 can be cylindrically shaped, a V-shaped groove or a funnel-shaped groove as described above. Holes are formed in silicon dioxide layer 208 so that leads 212 can be attached to regions 194, 198, 202 and 206 to couple voltage source 214, 216 and 218 and current meters 220, 222 and 224 to device 188 as will now be described. Voltage sources 214, 216 and 218 and current meters 220, 222 and 224 are similar to voltage source 112 and current meter 114, respectively, as described above.

Specifically, leads 212 couple voltage source 214 and current meter 220 in series to n-type doped silicon region 202 and n-type doped silicon region 206. Therefore, voltage source 214 applies a voltage across regions 202 and 206 which are separated by p-type silicon dioxide region 204. Leads 212 also couple voltage source 216 and current meter 222 to n-type doped silicon region 198 and n-type doped silicon region 202 as shown. Furthermore, leads 212 couple voltage source 218 and current meter 224 to n-type doped silicon region 194 and n-type doped silicon region 202 as shown. Accordingly, as can be appreciated from Figure 19, n-type doped silicon region 198 and n-type doped silicon region 194 act as the drain and source regions, respectively, of one MOSFET, n-type doped silicon region 202 and n-type doped silicon region 198 act as drain and source regions, respectively, of a second MOSFET, and n-type doped silicon region 206 and n-type doped silicon region 202 act as drain and source regions, respectively, of a third MOSFET. These three MOSFET type devices can measure the current induced by the bases of a DNA strand passing through opening 210, and thus take multiple measurements of these bases to improve accuracy.

It is also noted that a nucleic acid sequencing device above can be configured to sense the bases of a nucleic acid strand without it being necessary for the DNA strand to pass through an opening in the devices, as shown in Figs. 20 and 21. That is, using the techniques described above, a nucleic acid sequencing device 226, similar to nucleic acid sequencing device 102 shown in Figure 1, can be fabricated having its drain and source regions proximate to a surface. It is noted that like components shown in Figs. 1, 20 and 21 are identified with like reference numbers. However, in place of an opening 118, one or more grooves 228 can optionally be formed in the surface extending from the drain region to the source region. Alternatively, no grooves are formed in the surface, but rather, the detection area for detecting nucleic acid strands 111 is present between the drain and source regions. Techniques similar to those discussed above, such as the application of voltage potentials, by

means of voltage sources 117 and 121, and creation of a pressure differential in the container 108 can be used to move the nucleic acid strands 111 in a horizontal direction along the surface of the device over the grooves 228. The bases in the nucleic acid strands create an image charge channel 230 between the drain and source regions which allows current to flow between the drain and source regions. The current induced in the nucleic acid sequencing device by the bases can be measured in a manner similar to that described above.

Again, it is noted that the device 226 differs from the other embodiments represented in Figs. 1, 17 and 19 in that the channel 230 containing the image charge is horizontal rather than vertical. The structure no longer contains an opening 118 as in the device 102 shown in Figs. 1, 17 and 19, but rather this embodiment contains a charge sensitive region just above channel 230. Similar to Figure 1, the external electrodes 113 and 115 are used to apply an electric field which steers the nucleic acid strands 111 towards or away from the charge sensitive region. That is, the motion of the nucleic acid strands 111 is controlled by applying a voltage to the external electrodes 113 and 115 relative to the voltage applied to the doped regions 130. Additional electrodes (not shown) can be added to move the nucleic acid strands 111 perpendicular to the plane shown in Figure 20.

The charge sensitive region of the device is located just above the channel 230 and between the two doped regions 130. Identification of individual bases requires that the distance between the two doped regions is on the order of a single base and that the motion of the nucleic acid strand 111 is such that each base is successively placed above the charge sensitive region. This horizontal configuration enables more parallel as well as sequential analysis of the nucleic acid strands 111 and does not require the fabrication of a small opening. Additional surface processing, such as the formation of grooves 228 as discussed above that channel the nucleic acid strands 111 can be used to further enhance this approach.

The horizontal embodiment shown in Figs. 19 and 20 is also of interest to detect the presence of a large number of nucleic acid strands 111. For instance, using an electrophoresis gel as the medium, one starts by placing nucleic acid strands 111 of different length between the electrodes 113 and 115. A negative voltage is applied to the electrodes 113 and 115, relative to the doped regions 130. The nucleic acid strands 111 will then move towards the charge sensitive region. The smaller strands will move faster and the larger strands will move slower. The smaller strands will therefore arrive first at the charge sensitive region, followed by the larger ones. The charge accumulated in the charge sensitive region and therefore also

the image charge in the channel 230 therefore increases "staircase-like" with time. This results in a staircase-like increase or decrease of the current measured by current meter 114.

While this operation does not yield the identification of the individual bases of a single DNA/RNA strands, it does provide a measurement of the length of strands equivalent to the one obtained by an electrophoresis measurement. The advantage over standard electrophoresis is that a real-time measurement of the position of the DNA/RNA strands is obtained. In addition, the dimensions can be reduced dramatically since micron-sized devices can readily be made, while standard electrophoresis uses mm if not cm-sized drift regions. This size reduction leads to faster measurements requiring less DNA/RNA strands, while also reducing the cost of a single charge sensing device.

Although only several exemplary embodiments of the present invention have been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the following claims.

What is claimed is:

1. A system for detecting at least one polymer, comprising:
at least one semiconductor device having at least one detecting region, adapted to detect a charge representative of a component of said polymer proximate to said detecting region.
2. A system as claimed in claim 1, wherein:
said component includes a base in a nucleic acid strand; and
said detecting region is adapted to detect said charge representative of said base in said nucleic acid strand.
3. A system as claimed in claim 1, wherein:
said detecting region is further adapted to generate a signal representative of said detected charge.
4. A system as claimed in claim 1, wherein:
said detecting region includes a region of said semiconductor device defining an opening in said semiconductor device having a cross-section sufficient to enable said polymer to enter said opening, such that said detecting region is adapted to detect said charge of said component in said opening.
5. A system as claimed in claim 4, further comprising:
an excitation device, adapted to generate movement in said semiconductor device to facilitate movement of said polymer through said opening.
6. A system as claimed in claim 1, wherein:
said detecting region includes a region of said semiconductor device defining a recess in said semiconductor device, such that said detecting region is adapted to detect said charge of said component in said recess.
7. A system as claimed in claim 1, wherein:

said semiconductor device includes a plurality of said detecting regions; and
each said detecting region is adapted to detect a charge representative of a component of said at least one polymer proximate thereto.

8. A system as claimed in claim 1, wherein:

said semiconductor device further includes at least two doped regions; and
said detecting region is adapted to pass a current between said two doped regions in response to a presence of said component proximate to said detecting region.

9. A system as claimed in claim 1, wherein:

said semiconductor device includes a plurality of doped regions, and a respective detecting region associated with each respective pair of said doped regions, such that each said respective detecting region is adapted, in response to a presence of a component proximate thereto, to pass a respective current between its said respective pair of doped regions.

10. A system as claimed in claim 1, further comprising:
a plurality of said semiconductor devices.

11. A system as claimed in claim 1, further comprising:
a detector, adapted to detect a signal generated by said detecting region in response to said component proximate thereto.

12. A method for detecting at least one polymer, comprising the steps of:
positioning a portion of said polymer proximate to a detecting region of at least one semiconductor device; and
at said detecting region, detecting a charge representative of a component of said polymer proximate to said detecting region.

13. A method as claimed in claim 12, wherein:

said component includes a base in a nucleic acid strand; and

said detecting step detects said charge representative of said base in said nucleic acid strand.

14. A method as claimed in claim 12, further comprising the step of:
generating at said detecting region a signal representative of said detected charge.

15. A method as claimed in claim 12, wherein:
said detecting region includes a region of said semiconductor device defining an opening in said semiconductor device having a cross-section sufficient to enable said polymer to enter said opening; and
said detecting step detects said charge of said component in said opening.

16. A method as claimed in claim 15, further comprising the step of:
generating movement in said semiconductor device to facilitate movement of said polymer through said opening.

17. A method as claimed in claim 12, wherein:
said detecting region includes a region of said semiconductor device defining a recess in said semiconductor device; and
said detecting step detects said charge of said component in said recess.

18. A method as claimed in claim 12, wherein:
said semiconductor device includes a plurality of said detecting regions; and
said detecting step includes the step of detecting, at each said detecting region, a charge representative of a component of said at least one polymer proximate thereto.

19. A method as claimed in claim 12, wherein:
said semiconductor device further includes at least two doped regions; and
said method further includes the step of passing a current between said two doped regions in response to a presence of said component proximate to said detecting region.

20. A method as claimed in claim 12, wherein:

said semiconductor device includes a plurality of doped regions, and a respective detecting region associated with each respective pair of said doped regions: and

said method further includes the step of passing, at each said respective detecting region in response to a presence of a component proximate thereto, a respective current between its said respective pair of doped regions.

21. A method as claimed in claim 12, wherein:

said positioning step positions a respective portion of each of a plurality of said polymers proximate to a respective detecting region of a respective semiconductor device; and

said detecting step detects, at each said respective detecting region, a charge representative of a component of said respective polymer proximate to said respective detecting region.

22. A method as claimed in claim 12, further comprising the step of:

detecting a signal generated by said detecting region in response to said component proximate thereto.

23. A method for manufacturing a device for detecting a polymer, comprising the steps of:

providing a semiconductor structure comprising at least one semiconductor layer; and
creating a detecting region in said semiconductor structure, said detecting region being adapted to detect a charge representative of a component of said polymer proximate to said detecting region.

24. A method as claimed in claim 23, wherein:

said component includes a base in a nucleic acid strand; and
said creating step creates said detecting region which is adapted to detect said charge representative of said base in said nucleic acid strand.

25. A method as claimed in claim 23, further comprising the step of:

creating an opening in said semiconductor structure, said opening having a cross-section sufficient to enable a portion of said polymer to pass therethrough, and being positioned in relation to said detecting region such that said detecting region is adapted to detect said charge representative of said component in said opening.

26. A method as claimed in claim 25, wherein said opening creating step includes the step of:

forming an insulating layer on a wall of said semiconductor layer forming said opening to decrease said cross-section of said opening.

27. A method as claimed in claim 23, further comprising the step of:

creating a recess in said semiconductor structure, positioned in relation to said detecting region such that said detecting region is adapted to detect said charge representative of said component in said recess.

28. A method as claimed in claim 23, further comprising the steps of:

creating at least two doped regions in said semiconductor layer, said doped regions being positioned with respect to said detecting region such that said detecting region is adapted to pass a current between said doped regions in response to said component of said polymer proximate thereto.

29. A method as claimed in claim 28, wherein:

said doped region creating step creates said doped regions having a first doping such that said doped regions are separated by a portion of said semiconductor layer having a second doping.

30. A method as claimed in claim 28, wherein:

said doped region creating step creates said doped regions as a stack of doped regions, each having a first doping and being separated by a layer having a second doping.

31. A method as claimed in claim 28, wherein:

each of said doped regions includes a p-type doping.

32. A method as claimed in claim 28, wherein:
each of said doped regions includes an n-type doping.

AMENDED CLAIMS

[received by the International Bureau on 4 Octobre 2001 (04.10.01);
original claims 1-32 replaced by new claims 1-45 (7 pages)]

1. A system for detecting at least one polymer, comprising:
at least one semiconductor device having at least one detecting region, adapted to passively detect a charge of a component of said polymer proximate to said detecting region.
2. A system as claimed in claim 1, wherein:
said component includes a base in a nucleic acid strand; and
said detecting region is adapted to detect said charge representative of said base in said nucleic acid strand.
3. A system as claimed in claim 1, wherein:
said detecting region is further adapted to generate a signal representative of said detected charge.
4. A system as claimed in claim 1, wherein:
said detecting region includes a region of said semiconductor device defining an opening in said semiconductor device having a cross-section sufficient to enable said polymer to enter said opening, such that said detecting region is adapted to detect said charge of said component in said opening.
5. A system as claimed in claim 4, further comprising:
an excitation device, adapted to generate movement in said semiconductor device to facilitate movement of said polymer through said opening.
6. A system as claimed in claim 4, wherein:
said opening has a diameter within the range of about 1 nm to about 10 nm.
7. A system as claimed in claim 4, wherein:
said opening has a diameter of about 1 nm.
8. A system as claimed in claim 1, wherein:

said detecting region includes a region of said semiconductor device defining a recess in said semiconductor device, such that said detecting region is adapted to detect said charge of said component in said recess.

9. A system as claimed in claim 1, wherein:

said semiconductor device includes a plurality of said detecting regions; and
each said detecting region is adapted to detect a charge representative of a component of said at least one polymer proximate thereto.

10. A system as claimed in claim 1, wherein:

said semiconductor device further includes at least two doped regions; and
said detecting region is adapted to pass a current between said two doped regions in response to a presence of said component proximate to said detecting region.

11. A system as claimed in claim 1, wherein:

said semiconductor device includes a plurality of doped regions, and a respective detecting region associated with each respective pair of said doped regions, such that each said respective detecting region is adapted, in response to a presence of a component proximate thereto, to pass a respective current between its said respective pair of doped regions.

12. A system as claimed in claim 1, further comprising:
a plurality of said semiconductor devices.

13. A system as claimed in claim 1, further comprising:
a detector, adapted to detect a signal generated by said detecting region in response to said component proximate thereto.

14. A system as claimed in claim 1, wherein:

said at least one semiconductor device is adapted to passively detect said charge of said component without a portion of said semiconductor device binding with said component or chemically reacting with said component.

15. A system as claimed in claim 1, wherein:
said at least one semiconductor device is adapted to passively detect a single
said charge of said component.

16. A system as claimed in claim 1, wherein:
said at least one semiconductor device is adapted to passively detect said
charge of said component while said component is moving.

17. A method for detecting at least one polymer, comprising the steps of:
positioning a portion of said polymer proximate to a detecting region of at
least one semiconductor device; and
at said detecting region, passively detecting a charge of a component of said
polymer proximate to said detecting region.

18. A method as claimed in claim 17, wherein:
said component includes a base in a nucleic acid strand; and
said detecting step detects said charge representative of said base in said
nucleic acid strand.

19. A method as claimed in claim 17, further comprising the step of:
generating at said detecting region a signal representative of said detected
charge.

20. A method as claimed in claim 17, wherein:
said detecting region includes a region of said semiconductor device defining
an opening in said semiconductor device having a cross-section sufficient to enable
said polymer to enter said opening; and
said detecting step detects said charge of said component in said opening.

21. A method as claimed in claim 20, further comprising the step of:
generating movement in said semiconductor device to facilitate movement of
said polymer through said opening.

22. A method as claimed in claim 20, wherein:

said opening has a diameter within the range of about 1 nm to about 10 nm.

23. A method as claimed in claim 20, wherein:

said opening has a diameter of about 1 nm.

24. A method as claimed in claim 17, wherein:

said detecting region includes a region of said semiconductor device defining a recess in said semiconductor device; and

said detecting step detects said charge of said component in said recess.

25. A method as claimed in claim 17, wherein:

said semiconductor device includes a plurality of said detecting regions; and

said detecting step includes the step of detecting, at each said detecting region, a charge representative of a component of said at least one polymer proximate thereto.

26. A method as claimed in claim 17, wherein:

said semiconductor device further includes at least two doped regions; and

said method further includes the step of passing a current between said two doped regions in response to a presence of said component proximate to said detecting region.

27. A method as claimed in claim 17, wherein:

said semiconductor device includes a plurality of doped regions, and a respective detecting region associated with each respective pair of said doped regions; and

said method further includes the step of passing, at each said respective detecting region in response to a presence of a component proximate thereto, a respective current between its said respective pair of doped regions.

28. A method as claimed in claim 17, wherein:

said positioning step positions a respective portion of each of a plurality of said polymers proximate to a respective detecting region of a respective semiconductor device; and

said detecting step detects, at each said respective detecting region, a charge representative of a component of said respective polymer proximate to said respective detecting region.

29. A method as claimed in claim 17, further comprising the step of:
detecting a signal generated by said detecting region in response to said component proximate thereto.

30. A method as claimed in claim 17, wherein:
said detecting passively detects said charge of said component without a portion of said semiconductor device binding with said component or chemically reacting with said component.

31. A method as claimed in claim 17, wherein:
said detecting passively detects a single said charge of said component.

32. A method for manufacturing a device for detecting a polymer,
comprising the steps of:
providing a semiconductor structure comprising at least one semiconductor layer; and
creating a detecting region in said semiconductor structure, said detecting region being adapted to passively detect a charge of a component of said polymer proximate to said detecting region.

33. A method as claimed in claim 32, wherein:
said component includes a base in a nucleic acid strand; and
said creating step creates said detecting region which is adapted to detect said charge representative of said base in said nucleic acid strand.

34. A method as claimed in claim 32, further comprising the step of:
creating an opening in said semiconductor structure, said opening having a cross-section sufficient to enable a portion of said polymer to pass therethrough, and being positioned in relation to said detecting region such that said detecting region is adapted to detect said charge representative of said component in said opening.

35. A method as claimed in claim 34, wherein said opening creating step includes the step of:

forming an insulating layer on a wall of said semiconductor layer forming said opening to decrease said cross-section of said opening.

36. A method as claimed in claim 34, wherein:

said opening has a diameter within the range of about 1 nm to about 10 nm.

37. A method as claimed in claim 34, wherein:

said opening has a diameter of about 1 nm.

38. A method as claimed in claim 32, further comprising the step of:

creating a recess in said semiconductor structure, positioned in relation to said detecting region such that said detecting region is adapted to detect said charge representative of said component in said recess.

39. A method as claimed in claim 32, further comprising the steps of:

creating at least two doped regions in said semiconductor layer, said doped regions being positioned with respect to said detecting region such that said detecting region is adapted to pass a current between said doped regions in response to said component of said polymer proximate thereto.

40. A method as claimed in claim 39, wherein:

said doped region creating step creates said doped regions having a first doping such that said doped regions are separated by a portion of said semiconductor layer having a second doping.

41. A method as claimed in claim 39, wherein:

said doped region creating step creates said doped regions as a stack of doped regions, each having a first doping and being separated by a layer having a second doping.

42. A method as claimed in claim 39, wherein:

each of said doped regions includes a p-type doping.

43. A method as claimed in claim 39, wherein:
each of said doped regions includes an n-type doping.

44. A method as claimed in claim 32, wherein:
said detecting region is adapted to passively detect said charge of said component without a portion of said semiconductor device binding with said component or chemically reacting with said component.

45. A method as claimed in claim 32, wherein:
said detecting region is adapted to passively detect a single said charge of said component.

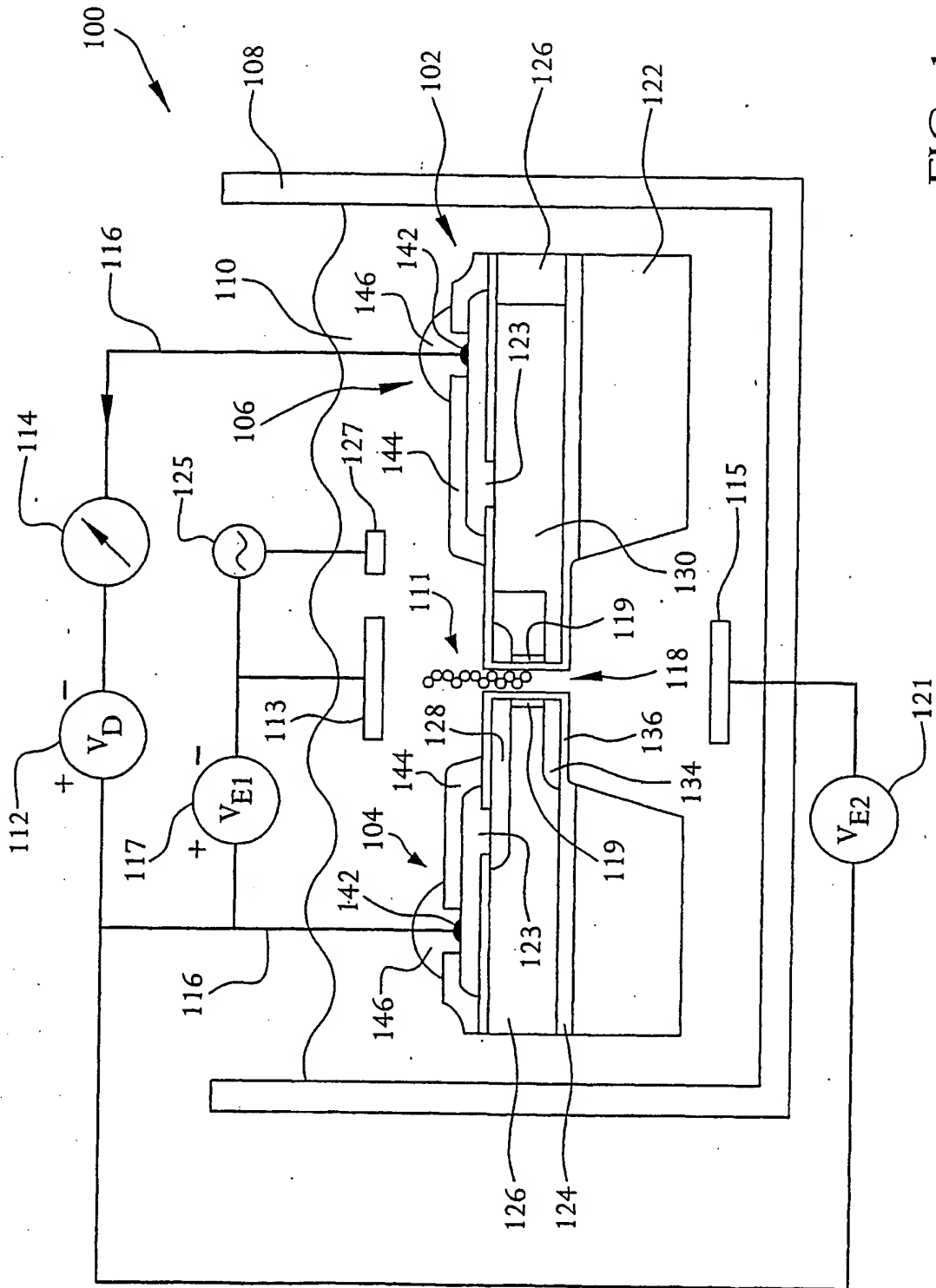


FIG. 1

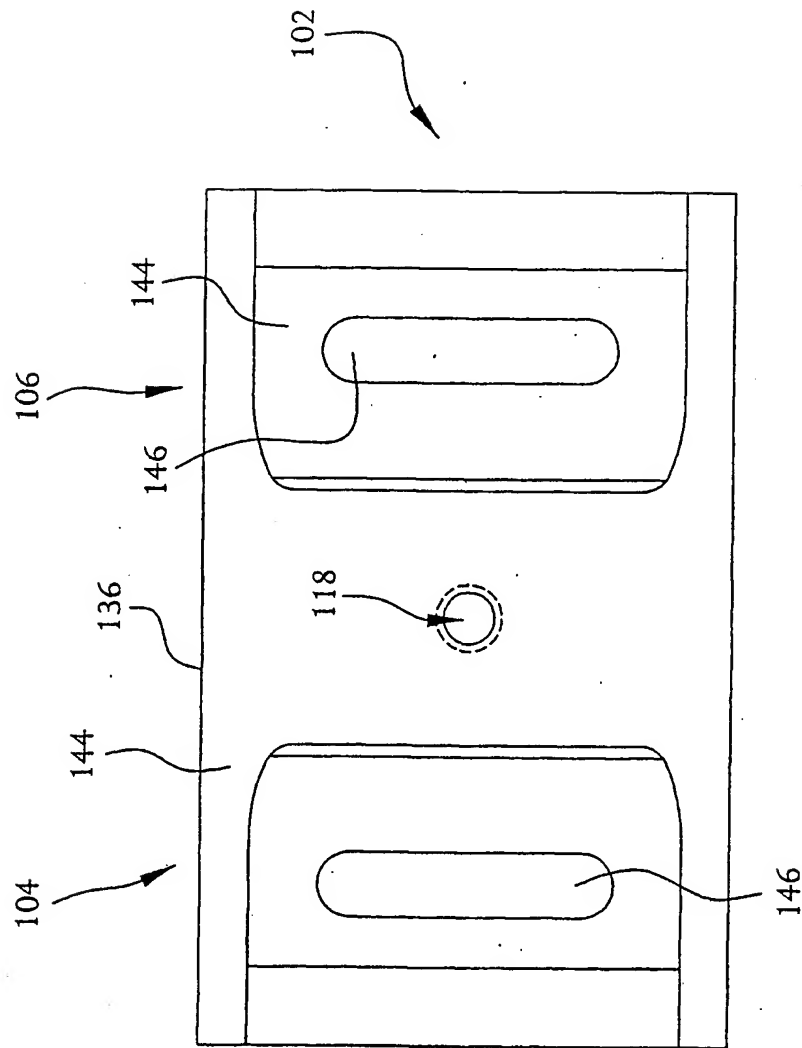


FIG. 2

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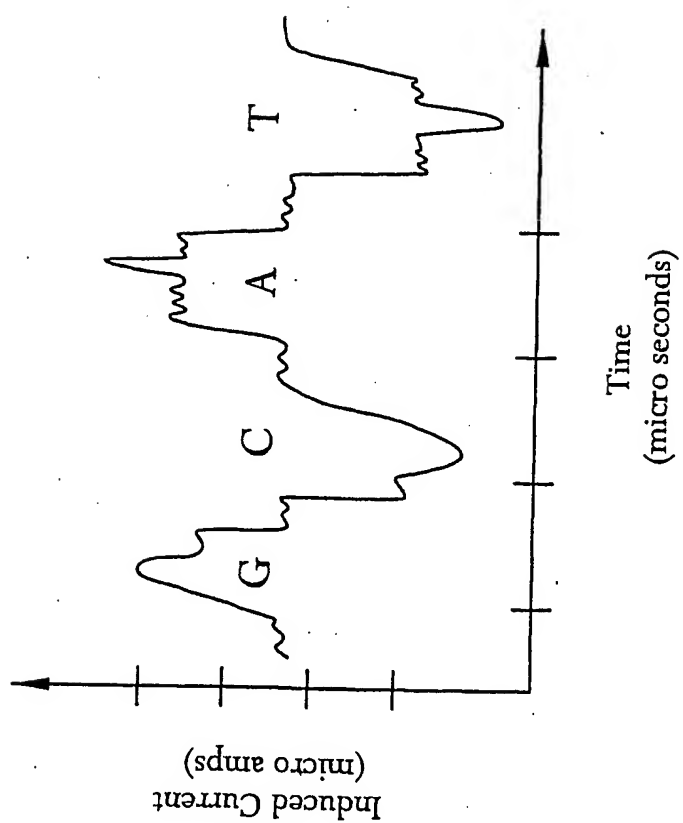


FIG. 3

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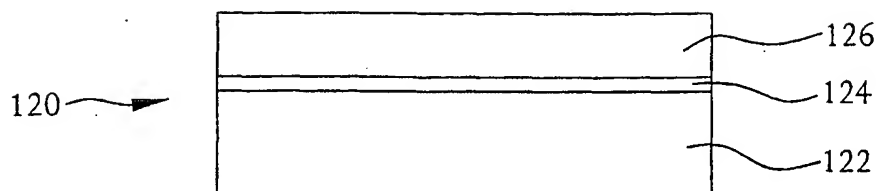


FIG. 4

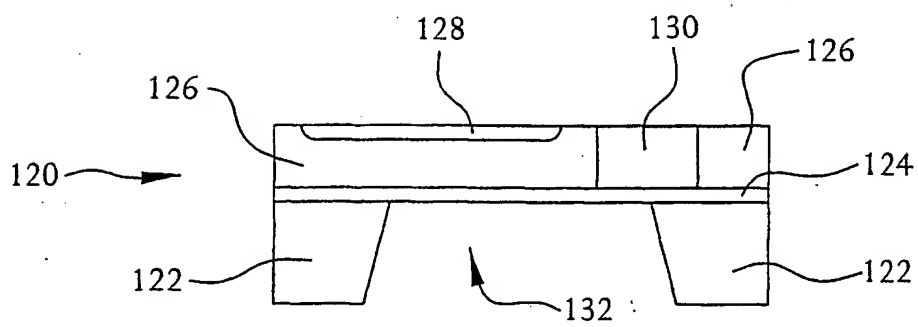


FIG. 5

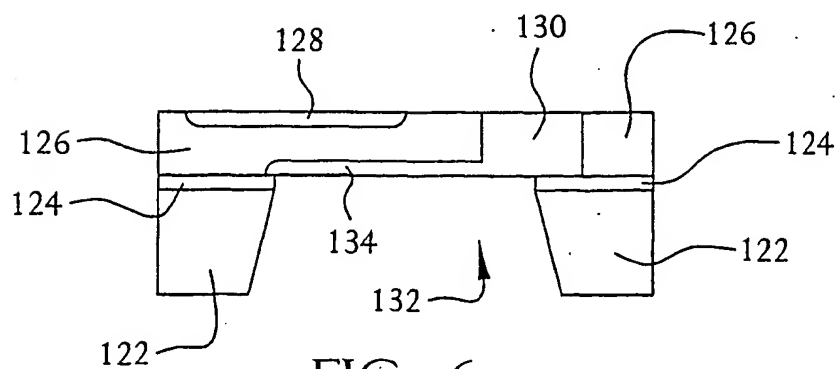


FIG. 6

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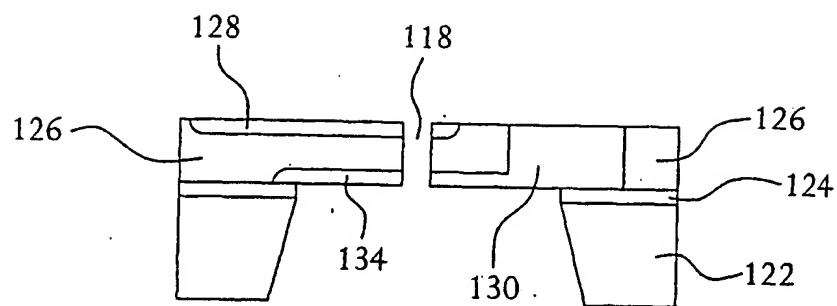


FIG. 7

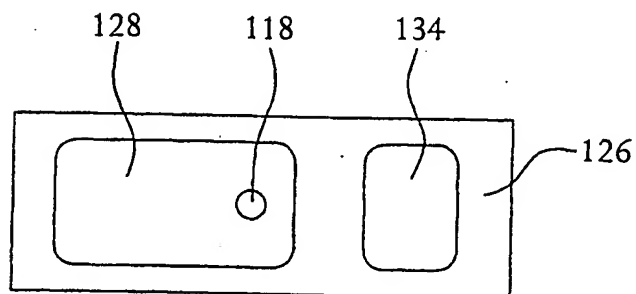


FIG. 8

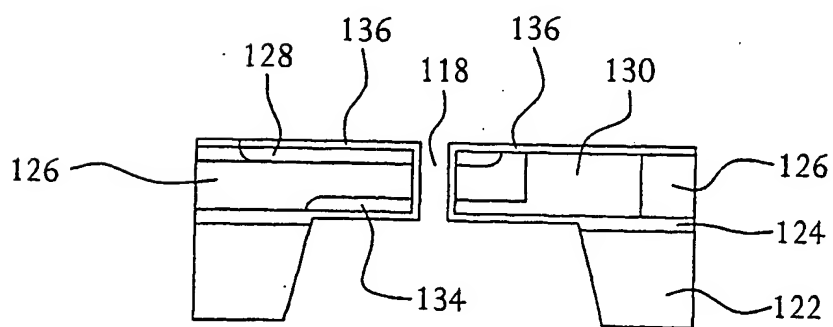


FIG. 9

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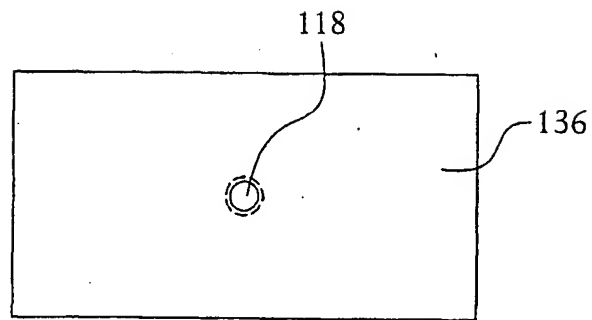


FIG. 10

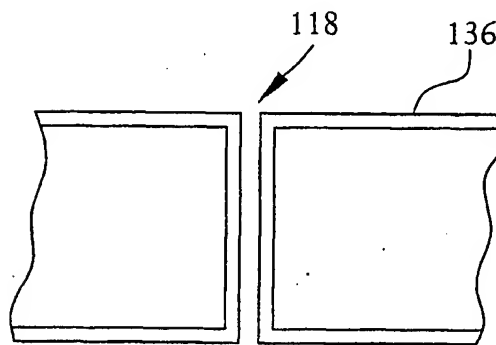


FIG. 11

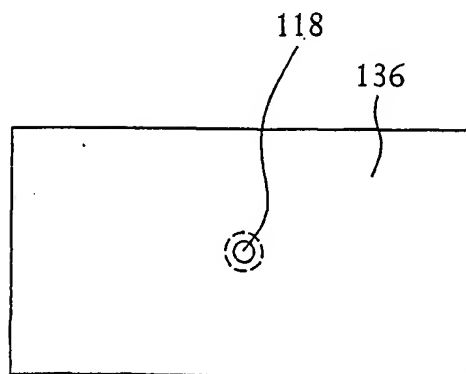


FIG. 12

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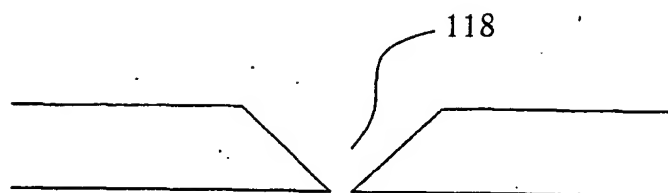


FIG. 13

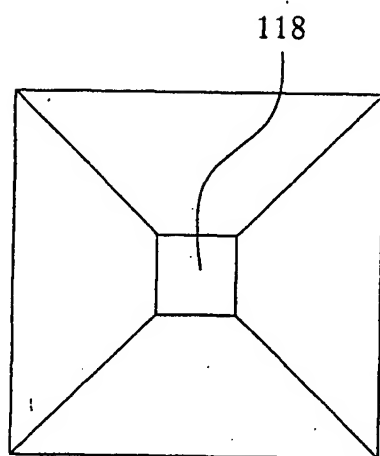


FIG. 14

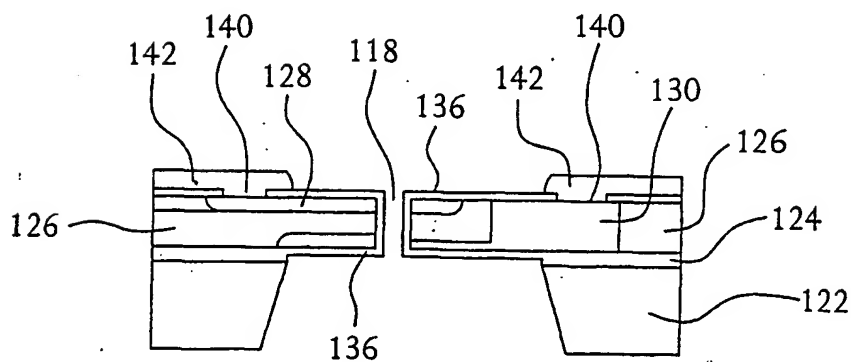


FIG. 15

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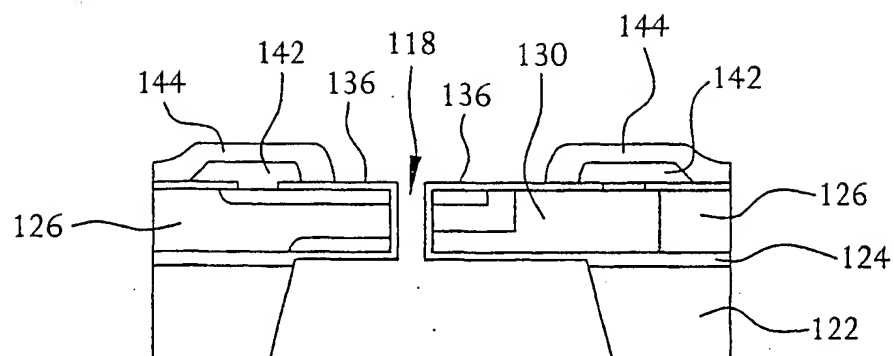


FIG. 16

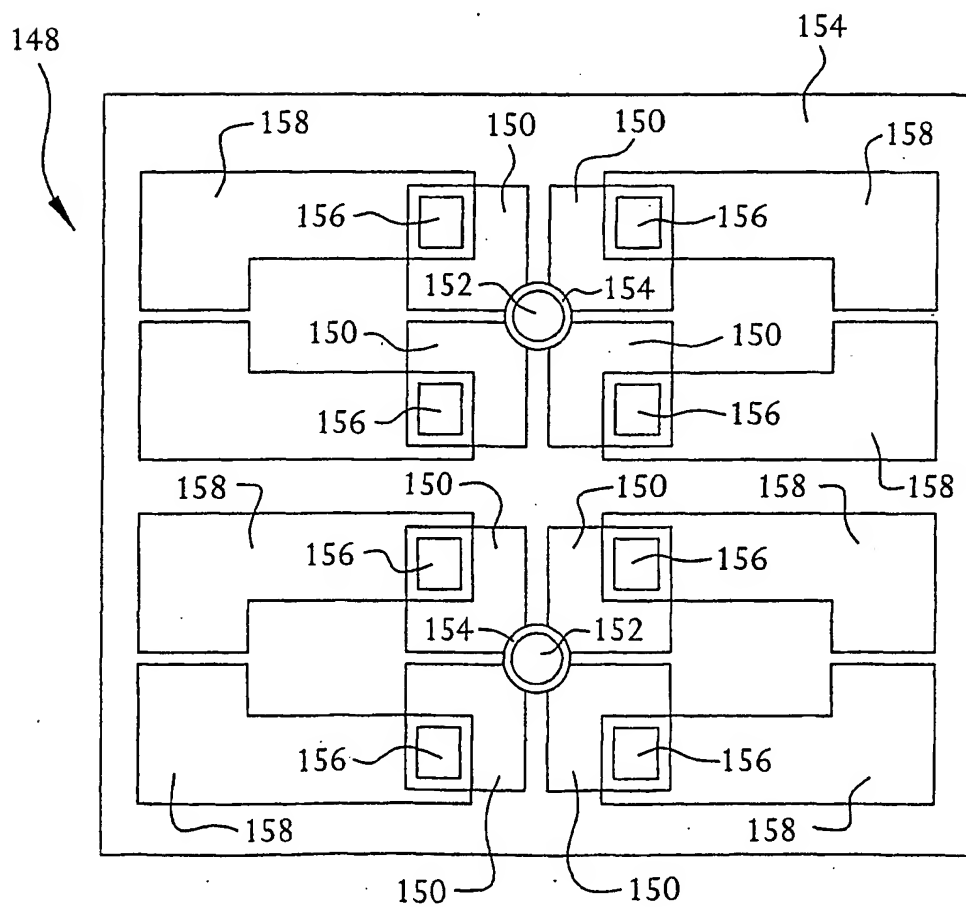


FIG. 17

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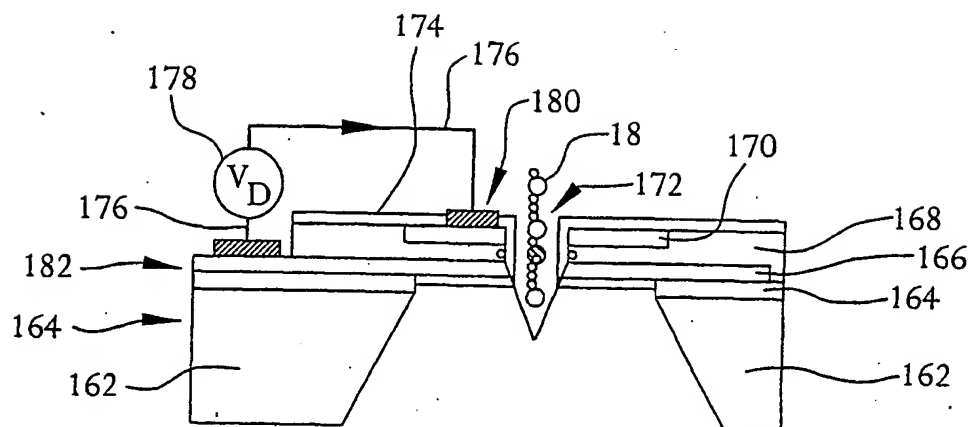


FIG. 18

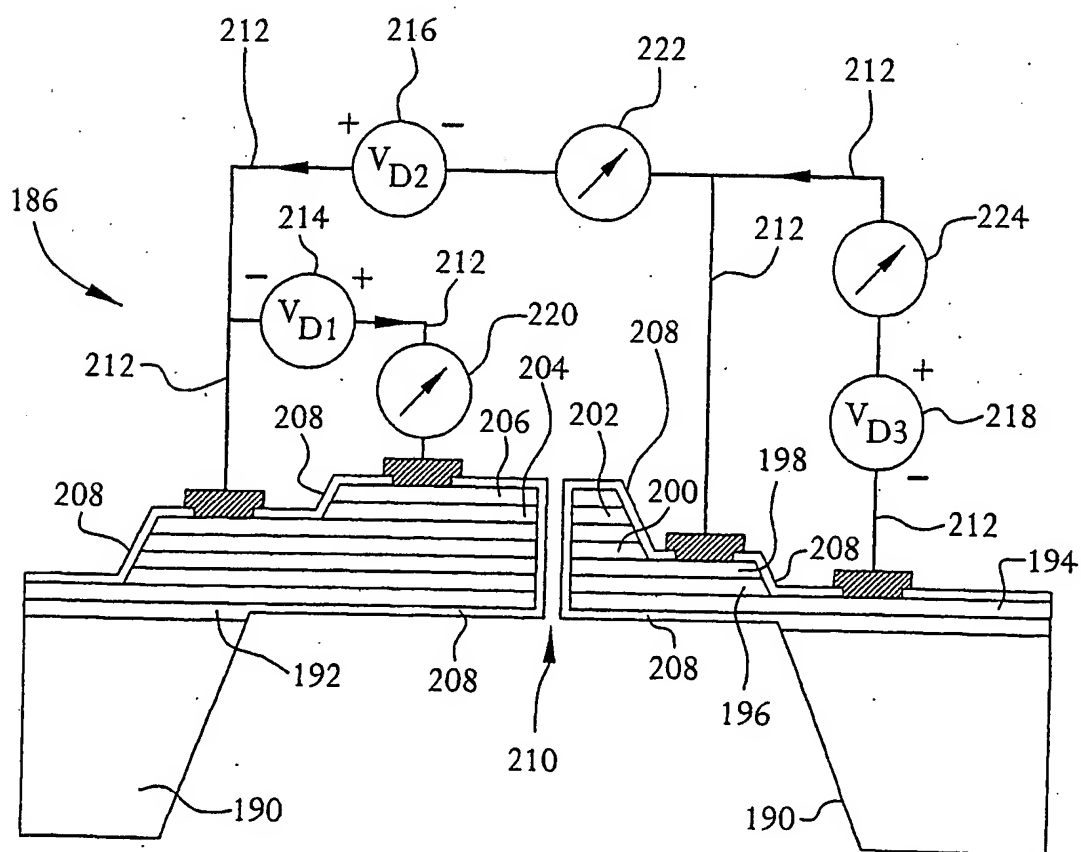


FIG. 19

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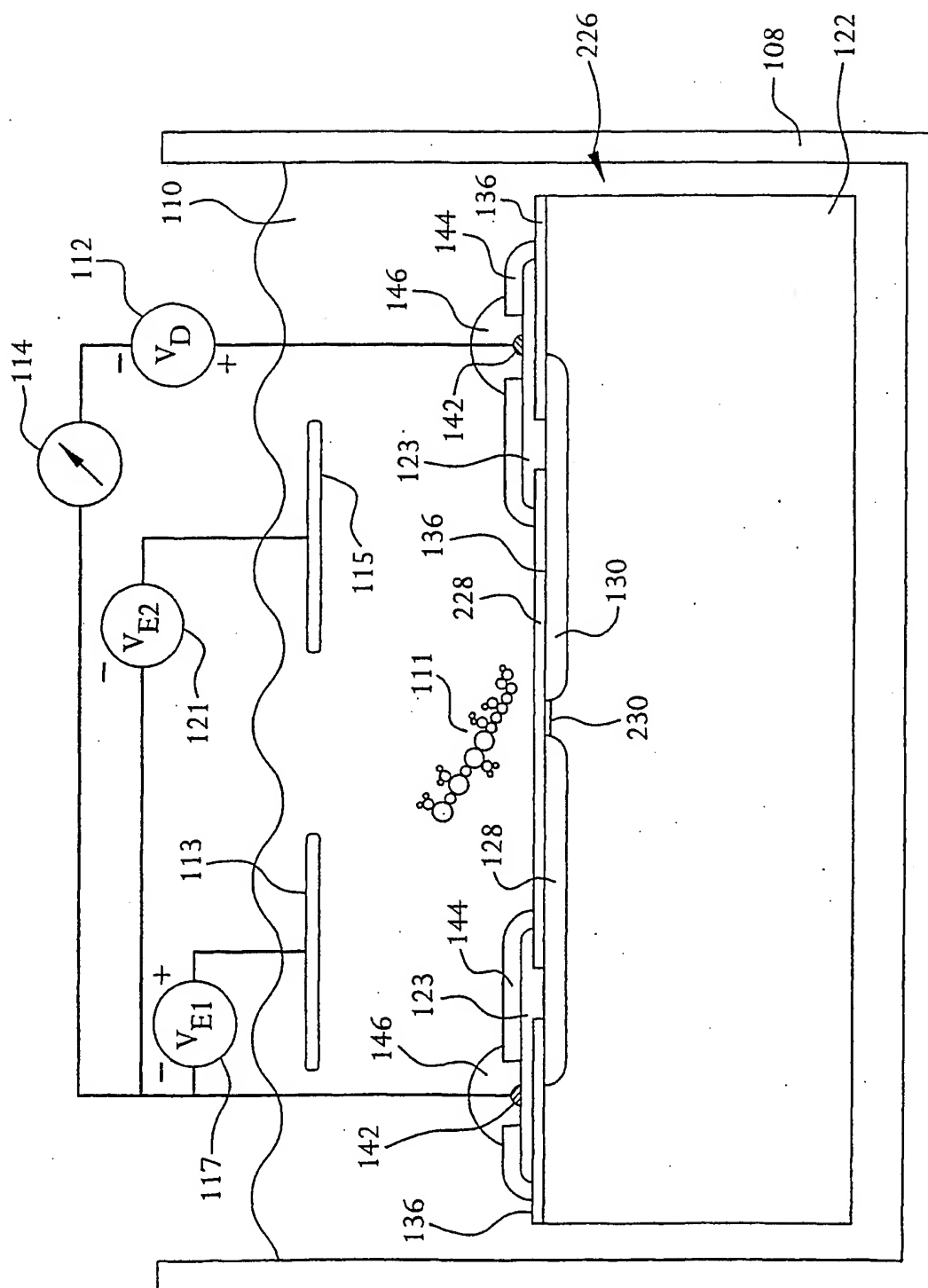


FIG. 20

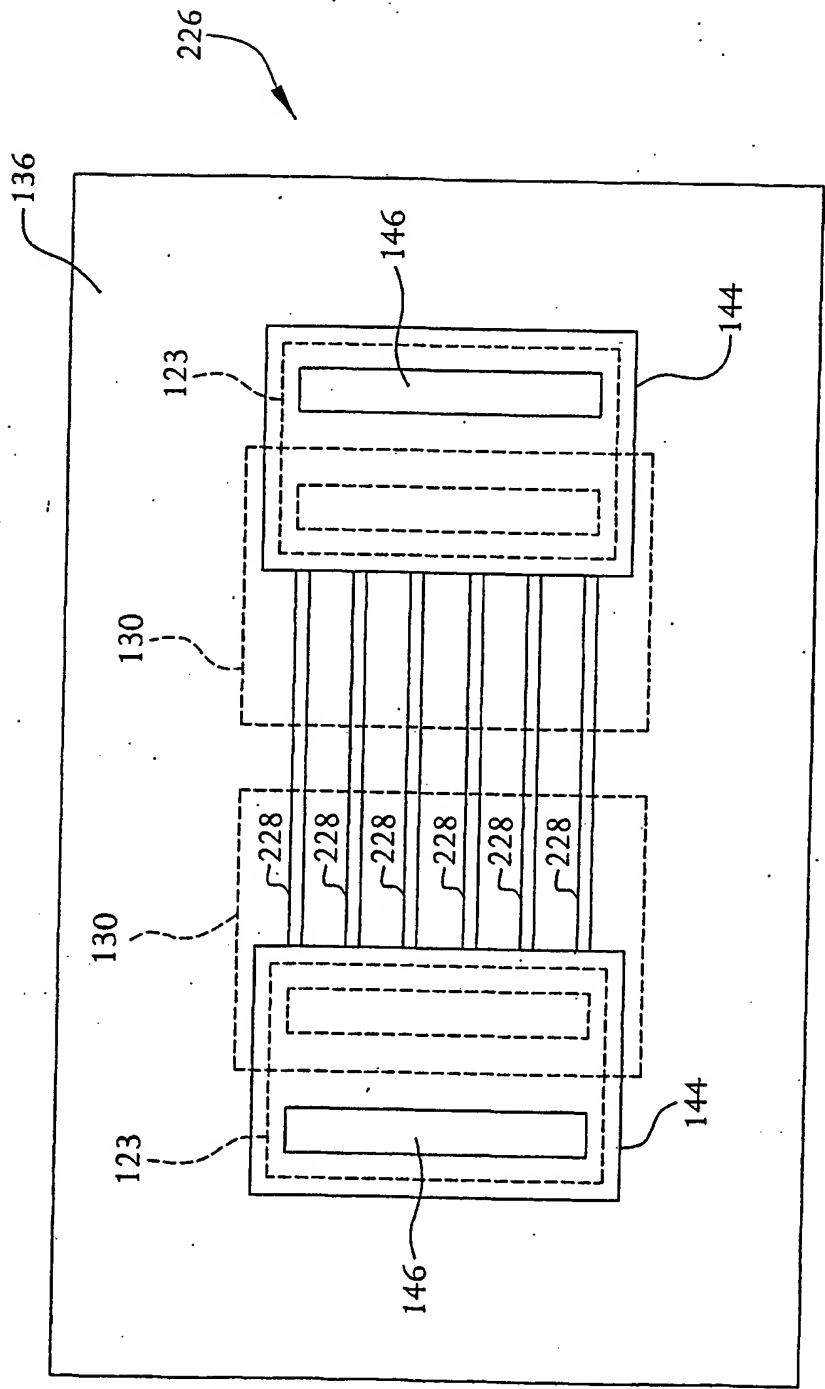


FIG. 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/13104

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : G01N 27/414; H01L 23/58, 21/00 US CL : 257/253; 438/49 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 257/253; 438/49; 435/6, 287.2; 204/450, 451, 455, 601; 436/72 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EAST search terms: DNA, RNA, nucleic acid, protein, biomolecule, CHEMFET, transistor, electrophoresis, channel, hole, pore, opening		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 4,777,019 A (Dandekar) 11 October 1988 (11.10.88), Abstract; col. 2, line 54 to col. 3, line 10; col. 4, lines 60-63; Fig. 1.	1-3, 7, 8, 11-14, 18, 19, 22-24, 28, 29, 32 ----- 6, 9, 10, 17, 20, 21, 27, 31
X — Y	US 4,238,757 A (Schenk) 9 December 1980 (9.12.80), Abstract, col. 4, lines 22-39; col. 5, lines 36-39; Fig. 3)	1, 3, 6-14, 17-24, 27-29, 31, 32 ----- 2
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *B* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *Z* document member of the same patent family		
Date of the actual completion of the international search 18 JULY 2001		Date of mailing of the international search report 06 AUG 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer: ERIK KIELIN <i>[Signature]</i> Telephone No. (703) 308-5980

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/13104

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,827,482 A (Shieh et al.) 27 October 1998 (27.10.98), Abstract; col. 2, lines 46-55; col. 3, lines 4-5; col. 7, lines 28-38; Fig. 1.	1-3, 7-14, 12-14, 18-24, 28, 29, 31, 32
Y	US 5,795,782 A (Church et al.) 18 August 1998 (18.08.98), Abstract; col. 1, lines 35-37; col. 3, line 66 to col. 4, line 12; col. 7, lines 7-14; Fig. 3.	1-32
Y	US 4,764,797 A (Shaw et al.) 16 August 1988 (16.08.88), Abstract, col. 2, line 62 to col. 3, line 10; col. 3, lines 39-54; col. 4, lines 58-66; col. 5, lines 44-49; all Figures.	1-32
X	US 5,466,348 A (Holm-Kennedy) 14 November 1995 (14.11.95), col. 9, line 48 to col. 10, line 8; Fig. 2B	1, 3, 6-14, 17-24, 27-29, 31, 32
X	US 5,869,244 A (Martin et al.) 02 February 1999 (09.02.99) Fig. 7; col. 7, lines 18-29; col. 8, lines 24-28.	1-3, 6-14, 17-24, 27-29, 31, 32
Y,P	US 6,176,990 B1 (Yager et al.), 23 January 2001 (23.01.01), Abstract; col. 2, lines 60-65; col. 9, line 60 to col. 10, line 20; all figures.	1-3, 6-14, 17-24, 27-29, 31, 32
Y,E	US 6,216,430 B1 (Yager et al.) 17 July 2001 (17.07.01), Abstract; col. 2, lines 60-65; col. 9, line 60 to col. 10, lines 20; all figures.	1-3, 6-14, 17-24, 27-29, 31, 32
Y	US 4,660,063 (Anthony) 21 April 1987 (21.04.87), Abstract; all figures, especially Figure 13.	1-32

